12. (Amended) The method of claim 9, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate, adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

Please add the following new claim.

37. (New) The method of claim 9, wherein steps (c) and (d) are repeated to identify a bi-ligand that binds to and has specificity for a third receptor in said receptor family.

REMARKS

Claims 9-14 are currently under examination. Claim 10 has been canceled. Claims 9, 11 and 12 have been amended. New claim 37 has been added. Support for the amendments and new claim can be found throughout the specification and the claims as filed. In particular, support for the amendment to claim 9 can be found, for example, on page 11, lines 6-13, which indicates that a receptor can be an enzyme; and on page 8, lines 29-31, and page 13, line 32, to page 14, line 2, which indicates that a common ligand binds to a conserved site and that a conserved site of an enzyme is a site that binds a cofactor. Support for new claim 37 can be found, for example, in original claims 9 and 10 and on page 15, line 14, to page 16, line 15, which teaches methods to identify a population of bi-ligands by screening and

identifying a bi-ligand that binds to and has specificity for a first receptor and a bi-ligand that has specificity for a second receptor; and on page 16, lines 23-28, page 47, lines 7-15, and Figure 1, which teaches that a population of bi-ligands can be used to screen for ligands that bind to other members of the receptor family. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant has set forth the amendment to the specification and claims in clean form in Appendix A, with marked up amendments indicated with brackets and underlining.

Applicant appreciates Examiner Garcia's time and helpful discussion with Applicant and Applicant's representatives in the interview on January 18, 2002. Applicant believes the amendments and evidence presented herein addresses the issues discussed with the Examiner.

Applicant wishes to bring to the Examiner's attention co-pending application serial Nos. 09/083,537; 09/328,322; 09/354,811; and 09/765,693.

Regarding the Petition to Make Special

Applicant wishes to bring to the Examiner's attention that a Petition to Make Special was filed in the above-identified application on September 21, 2001. Examiner Garcia has indicated that the Petition to Make Special has not been entered in the case. For the convenience of the Examiner, Applicant encloses a

copy of the Petition to Make Special, along with the postcard showing that the Petition was received at the USPTO on October 2, 2001.

Regarding the Information Disclosure Statement

The Office Action indicates that the Information Disclosure Statement (IDS) filed on May 7, 2001, has been considered but indicates that the file history appears to indicate another IDS was filed on May 3, 2001. To clarify the record, an IDS was mailed by Applicant on April 30, 2001, and this IDS corresponds to the PTO-1449 considered and signed by the Examiner and forwarded in the present Office Action. Therefore, the Examiner appears to have considered the references filed by Applicant in an IDS.

Objection to the Specification

The Office Action indicates that the specification contains embedded hyperlink text. The specification has been amended to delete "http" and "ftp" from internet addresses to remove any hyperlinking capability of the text. Accordingly, Applicant respectfully requests that the objection to the specification be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 9-14 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description is

respectfully traversed. Applicant submits that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed.

Claim 9, as amended, is directed to a method for identifying a population of bi-ligands to receptors in a receptor family. The method includes the steps of attaching an expansion linker to a common ligand, wherein the common ligand binds to a cofactor binding site and wherein the expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in the receptor family, to form a module, wherein the receptor is an enzyme; generating a population of bi-ligands, wherein the bi-ligand comprises the module and a second ligand linked by the expansion linker; screening the population of bi-ligands for binding to a receptor in the receptor family; identifying a bi-ligand that binds to and has specificity for the receptor; and repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second receptor in the receptor family.

Applicant respectfully submits that the specification provides sufficient description and guidance to convey that Applicant was in possession of the claimed invention. Moreover, Applicant has amended claim 9 to recite that the common ligand binds to a cofactor binding site. Claim 9 has also been amended to indicate that the receptor is an enzyme. The specification teaches numerous exemplary receptors that are enzymes (page 11, line 6, to page 13, line 6). The specification also teaches that

a "common ligand" binds to a conserved site in a receptor family (page 8, lines 29-31) and that a conserved site in an enzyme can be a site that binds a cofactor (page 13, line 32, to page 14, line 2). Applicant respectfully submits that one skilled in the art, based on the teachings in the specification, would have understood the meaning of the terms recited in the claims and that Applicant was in possession of the claimed invention at the time the application was filed.

Applicant respectfully disagrees with the assertion in the Office Action on page 6, paragraph 2, that the specification discloses no examples of the preparation and use of a "population of bi-ligands." The specification teaches that a bi-ligand is identified by determining a common ligand that binds to at least two target receptors in a receptor family (page 29, lines 7-9). The specification also teaches methods of identifying a common ligand, for example, by selecting candidate compounds based on structural similarities, screening of commercially available compounds, or using structural information and commercially available databases to identify common ligands (page 31, line 23, to page 32, line 25). The specification additionally teaches that a common ligand can be identified by screening for competitive binding to a natural common ligand (page 30, line 29, to page 31, line 22; and page 32, lines 26-30).

The specification further teaches that methods such as NMR can be applied to identify sites on a common ligand proximal to a specificity site (page 34, line 5, to page 39, line 17). The specification also teaches that an expansion linker is

attached to the common ligand so that the expansion linker is oriented towards the specificity site (page 39, line 18, to page 43, line 6) and that a bi-ligand is generated by attaching potential specificity ligands having reactive groups to the expansion linker at the position on the expansion linker that orients the specificity ligand to the specificity site (page 43, lines 19-27). The specification additionally teaches that a population of bi-ligands can be used to identify ligands for a receptor in a receptor family and therapuetic agents (page 16, line 16, to page 19, line 13). Accordingly, Applicant submits that the specification provides examples of how to make and use populations of bi-ligands and the claimed methods of identifying such a population of bi-ligands.

In view of the teachings in the specification, Applicant submits that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 9-14 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicant submits that the specification provides sufficient description and guidance to enable the claimed invention.

Regarding the breadth of the claims, Applicant submits that one skilled in the art, based on the teachings in the

specification, would have understood how to make and use the invention as claimed. Claim 9, as amended, to is directed to a method for identifying a population of bi-ligands by attaching an expansion linker to a common ligand, wherein the common ligand binds to a cofactor binding site and wherein the expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in the receptor family, to form a module, wherein the receptor is an enzyme; generating a population of bi-ligands, wherein the bi-ligand comprises the module and a second ligand linked by the expansion linker; screening the population of bi-ligands for binding to a receptor in the receptor family; identifying a bi-ligand that binds to and has specificity for the receptor; and repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second receptor in the receptor family.

The specification teaches numerous exemplary receptors that are enzymes (page 11, line 6, to page 13, line 6). The specification also teaches that a "common ligand" binds to a conserved site in a receptor family (page 8, lines 29-31) and that a conserved site in an enzyme can be a site that binds a cofactor (page 13, line 32, to page 14, line 2). The specification additionally teaches numerous exemplary enzyme cofactors (page 12, line 31, to page 13, line 6; and original claims 6, 12, 17, 24, 29 and 34). Therefore, Applicant submits that the specification provides sufficient description and guidance to enable the claimed methods for identifying a population of bi-ligands containing a common ligand that binds to a cofactor binding site of an enzyme.

With regard to the lack of working examples, Applicant respectfully points out that working examples are not required. Furthermore, the specification provides examples of how to make and use the invention, as claimed. As discussed above, the specification teaches that a bi-ligand is identified by determining a common ligand that binds to at least two target receptors in a receptor family (page 29, lines 7-9). The specification also teaches methods of identifying a common ligand, for example, by selecting candidate compounds based on structural similarities, screening of commercially available compounds, or using structural information and commercially available databases to identify common ligands (page 31, line 23, to page 32, line 25). The specification additionally teaches that a common ligand can be identified by screening for competitive binding to a natural common ligand (page 30, line 29, to page 31, line 22; and page 32, lines 26-30).

The specification further teaches that methods such as NMR can be applied to identify sites on a common ligand proximal to a specificity site (page 34, line 5, to page 39, line 17). The specification also teaches that an expansion linker is attached to the common ligand so that the expansion linker is oriented towards the specificity site (page 39, line 18, to page 43, line 6) and that a bi-ligand is generated by attaching potential specificity ligands having reactive groups to the expansion linker at the position on the expansion linker that orients the specificity ligand to the specificity site (page 43, lines 19-27). The specification additionally teaches that a population of bi-ligands can be used to identify ligands for a

receptor in a receptor family and therapuetic agents (page 16, line 16, to page 19, line 13). Accordingly, Applicant submits that the specification provides examples of how to make and use the claimed population of bi-ligands. Therefore, Applicant submits that the specification provides sufficient description and guidance to enable one skilled in the art to make and use the invention as claimed.

Further in support of the enablement of the claimed invention, Applicant submits herewith a Rule 132 Declaration (Exhibit 1) providing corroborative evidence for the enablement of the claimed methods of identifying a population of bi-ligands. The attached Declaration provides exemplary evidence that the teachings in the specification are sufficient to enable one skilled in the art to make and use the claimed population of bi-ligands.

In the attached Declaration (Exhibit 1), Dr. Sem describes the generation of a population of bi-ligands using the teachings in the specification. Computational methods were used to identify potential common ligands, and the potential common ligands were obtained from commercially available sources, as taught on page 32, lines 6-25. A common ligand was identified using competitive binding assays, as taught on page 30, line 29, to page 31, line 10; and page 32, lines 26-30. NMR experiments were used to determine amino acid residues proximal to a specificity site using a natural common ligand, and the binding and orientation of a common ligand relative to the specificity site was determined, as taught on page 34, line 5, to page 39,

line 17. A bi-ligand library of about 3200 compounds was generated and screened for binding to an enzyme receptor family that binds to NADH/NADPH, as taught, for example, on page 43, lines 19-27; and page 45, lines 1-25. A population of bi-ligands was generated and bi-ligands were identified having specificity for a first receptor and second receptor, as taught on page 45, line 18, to page 46, line 12. Specifically, the Declaration describes an exemplary population of bi-ligands containing a bi-ligand having specificity for LDH over DHPR and DOXPR and another bi-ligand having specificity for DOXPR over LDH and DHPR. Applicant submits that the evidence provided in the attached Declaration corroborates the teachings in the specification on how to make and use a population of bi-ligands and methods of identifying such a population.

Regarding the receptor family exemplified in the Declaration attached as Exhibit 1, the receptor family, of which DHPR, LDH and DOXPR are representative members, is a receptor family that binds nicotinamide adenine dinucleotide. The specification teaches that members of a receptor family bind a natural common ligand, for example, NADH/NADPH, and that such binding can be verified in a binding assay (page 13, lines 21-23). As indicated in the Declaration attached as Exhibit 1, DHPR, LDH and DOXPR were assayed for bi-ligand binding using a competitive assay for binding of NADH or NADPH. Therefore, DHPR, LDH and DOXPR are members of the same receptor family in that they bind a natural common ligand, as taught in the specification.

In view of the teachings in the specification, and as corroborated by the evidence presented as Exhibits 1 and A-C, Applicant submits that the specification provides sufficient description and guidance to enable the claimed methods of identifying a population of bi-ligands. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claim 11 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. The Office Action indicates that the term "receptor" is indefinite because it lacks clear antecedent basis. Applicant has amended claim 11 to recite "said receptor in said receptor family is an enzyme." Applicant submits that the term "receptor" has clear antecedent basis and respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

The rejection of claims 9-14 under 35 U.S.C. § 102(b) as allegedly anticipated by Combs et al., J. Am. Chem. Soc. 118:287-288 (1996), is respectfully traversed. Applicant submits that these claims are novel over Combs et al.

Claim 9, as amended, to is directed to a method for identifying a population of bi-ligands by attaching an expansion linker to a common ligand, wherein the common ligand binds to a cofactor binding site and wherein the expansion linker has

sufficient length and orientation to direct a second ligand to a specificity site of a receptor in the receptor family, to form a module, wherein the receptor is an enzyme; generating a population of bi-ligands, wherein the bi-ligand comprises the module and a second ligand linked by the expansion linker; screening the population of bi-ligands for binding to a receptor in the receptor family; identifying a bi-ligand that binds to and has specificity for the receptor; and repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second receptor in the receptor family.

In contrast to the claimed invention, Combs et al. does not teach a method of identifying a population of bi-ligands containing a common ligand that binds to a cofactor binding site of an enzyme, as claimed. Combs et al., at best, appears to describe ligands that bind to a single site, the SH3 domain of Src, not a cofactor binding site of an enzyme. Absent a teaching of the claimed population of bi-ligands containing a common ligand that binds to a cofactor binding site of an enzyme, Combs et al. cannot anticipate the claims. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 9-14 under 35 U.S.C. § 102(b) as allegedly anticipated by He et al., Bioorg. Med. Chem. Lett. 4:2845-2850 (1994), is respectfully traversed. Applicant submits that these claims are novel over He et al.

In contrast to the claimed invention, He et al. does not teach a method of identifying a population of bi-ligands

containing a bi-ligand that binds to and has specificity for a first receptor and a bi-ligand that binds to and has specificity for a second receptor. In this regard, the specification teaches that a ligand exhibiting specificity for a receptor in a receptor family differentially binds to a particular receptor, which is measurably higher than the binding of the ligand to at least one other receptor in the same family (page 45, lines 26-30). The specification further teaches that a ligand having 2-fold higher affinity or greater for one receptor over another receptor in the same family is considered to have specificity for binding to that receptor (page 45, line 30, to page 46, line 1). Thus, the specification teaches that a bi-ligand having specificity for a receptor refers to differential binding of 2-fold higher affinity or greater for one receptor over another receptor in the same receptor family.

In contrast to the claimed invention, He et al., at best, appears to describe compounds that have specificity for one receptor over another, that is, specificity for protein kinase C (PKC) over protein kinase A (PKA). However, none of compounds 5 through 16 of He et al., which contain a core structure with variable R groups, have specificity for a second receptor, that is, none of the compounds exhibit specificity for PKA over PKC. In particular, note that the IC_{50} values shown in Table 1 of He et al. are all lower (that is, higher affinity) for PKC than for PKA. To more clearly illustrate that the compounds described by He et al. have specificity for only one receptor, at best, attached herewith as Exhibit 2 is a table reproducing the portion of Table 1 of He et al. showing the activity of compounds 5

through 16 for PKC and PKA. In the attached table, an additional column has been included which shows the fold higher affinity of PKC over PKA, which was calculated by dividing the IC_{50} values for PKA by the IC_{50} values for PKC.

As shown in Exhibit 2, compounds 5, 7 and 16 appear to have no specificity for PKC or PKA, that is, there is less than a 2-fold difference in affinity between these two enzymes. Compounds 6, 8 through 10, and 13 through 15 exhibited from at least 2-fold to almost 40-fold higher affinity for PKC over PKA. Compounds 11 and 12 showed no inhibition of PKA and therefore appear only to have binding activity for PKC. Therefore, of the compounds described in He et al., none exhibited specificity for a second receptor in the receptor family. Absent the teaching in He et al. of a method of identifying population of bi-ligands containing a bi-ligand having specificity for a first receptor and a bi-ligand having specificity for a second receptor in a receptor family, He et al. cannot anticipate the claims. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

February 25, 2002
Date

Deborah L. Cadena
Registration No. 44,048
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122
USPTO CUSTOMER NO. 23601

Inventor: Daniel S. Sem
Serial No.: 09/765,696
Filed: January 19, 2001

APPENDIX A

In the Specification:

On page 11, please delete the paragraph on lines 14-32 and substitute therefor:

Enzymes can also be classified based on Enzyme Commission (EC) nomenclature recommended by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB) (see, for example, [http://]www.expasy.ch/sprot/enzyme.html)(which is incorporated herein by reference). For example, oxidoreductases are classified as oxidoreductases acting on the CH-OH group of donors with NAD' or NADP' as an acceptor (EC 1.1.1); oxidoreductases acting on the aldehyde or 0x0 group of donors with NAD' or NADP+ as an acceptor (EC 1.2.1); oxidoreductases acting on the CH-CH group of donors with NAD+ or NADP' as an acceptor (EC 1.3.1); oxidoreductases acting on the CH-NH, group of donors with NAD+ or NADP+ as an acceptor (EC 1.4.1); oxidoreductases acting on the CH-NH group of donors with NAD' or NADP+ as an acceptor (EC 1.5.1); oxidoreductases acting on NADH or NADPH (EC 1.6); and oxidoreductases acting on NADH or NADPH with NADC or NADP+ as an acceptor (EC 1.6.1).

On page 19, please delete the paragraph on page 19, line 25, to page 20, line 10, and substitute therefor:

Methods for determining that two receptors are in the same family are well known in the art. For example, one method for determining if two receptors are related is BLAST, Basic Local Alignment Search Tool, available on the National Center for Biotechnology Information web page ([http://]www.ncbi.nlm.gov/BLAST/)(which is incorporated herein by reference). BLAST is a set of similarity search programs designed to examine all available sequence databases and can function to search for similarities in protein or nucleotide sequences. A BLAST search provides search scores that have a well-defined statistical interpretation. Furthermore, BLAST uses a heuristic algorithm that seeks local alignments and is therefore able to detect relationships among sequences which share only isolated regions of similarity (Altschul et al., J. Mol. Biol. 215:403-410 (1990), which is incorporated herein by reference).

On page 20, please delete the paragraph on page 20, line 27, to page 21, line 16, and substitute therefor:

A second resource for identifying members of a receptor family is PROSITE, available at ExPASy ([http: //] www.expasy.ch/sprot/prosite.html) (which is incorporated herein by reference). PROSITE is a method of determining the function of uncharacterized proteins translated from genomic or cDNA sequences (Bairoch et al., Nucleic Acids Res. 25:217-221 (1997) I which is incorporated herein by reference). PROSITE

consists of a database of biologically significant sites and patterns that can be used to identify which known family of proteins, if any, the new sequence belongs. In some cases, the sequence of an unknown protein is too distantly related to any protein of known structure to detect its resemblance by overall sequence alignment. However, related proteins can be identified by the occurrence in its sequence of a particular cluster of amino acid residues, which can be called a pattern, motif, signature or fingerprint. PROSITE uses a computer algorithm to search for motifs that identify proteins as family members. PROSITE also maintains a compilation of previously identified motifs, which can be used to determine if a newly identified protein is a member of a known protein family.

On page 21, please delete the paragraph on lines 17-25 and substitute therefor:

A third resource for identifying members of a receptor family is Structural Classification of Proteins (SCOP) available at SCOP ([http://]scop.mrc-lmb.cam.ac.uk/scop/)(which is incorporated herein by reference). Similar to PROSITE, SCOP maintains a compilation of previously determined protein motifs for comparison and determination of related proteins (Murzin et al., J. Mol. Biol. 247:536-540 (1995), which is incorporated herein by reference).

On page 22, after "**SEARCHABLE MOTIF AND PATTERN DATABASES**" and "**WEBSITES**" on lines 3-4, please delete lines 5-11 and substitute therefor:

PROSITE [http://]expasy.hcuge.ch/sprot/prosite.html

BLOCKS [http://]www.blocks.fhcrc.org/blocks_search.html

PRINTS [http://]www.biochem.ucl.ac.uk/bsm/dbbrowser/PRINTS/PRINTS.html

PIMA [http://]dot.imgen.bcm.tmc.edu:9331/seq-search/protein- search.html

PRODOM [http://]protein.toulouse.inra.fr/prodom.html

On page 22, after "**MOTIF AND PROFILE SEARCHES**" and "**WEBSITES**" on line 12, please delete lines 13-22 and substitute therefor:

REGULAR EXPRESSION SEARCH [http://]www.ibc.wustl.edu/fpat/

PROFILESEARCH [http://]www.seqnet.dl.ac.uk/hhg/PROFILESE.html

PATSCAN [http://]www-c.mcs.anl.gov/home/overbeek/PatScan/HTML/patscan.html

PATTERNFIND [http://]ulrec3.unil.ch/software/PATFND-mailform.html

PROFILE [http://]lenti.med.umn.edu/MolBio_man/chp-10.html#HDR1

On page 23, please delete lines 1-2 and substitute therefor:

PMOTIF [http://]alces.med.umn.edu/pmotif.html

HMMER [http://]genome.wustl.edu/eddy/HMMER/

On page 23, after "**WWW AND FTP SERVERS FOR SINGLE SEQUENCE EXHAUSTIVE DATABASE SEARCHES**" and "**WEBSITES**" on lines 3-5, please delete lines 6-8 and substitute therefor:

BLAST [http://]www.ncbi.nlm.nih.gov/BLAST/

BLITZ [http://]www.ebi.ac.uk/searches/blitz_input.html

FASTA [http://]www.genome.ad.jp/ideas/fasta/fasta_genes.html

On page 23, after "**FTP ADDRESSES FOR MOTIF AND PROFILE SEARCH PROGRAMS**" and "**WEBSITES**" on lines 9-10, please delete lines 11-17 and substitute therefor:

BARTON'S FLEXIBLE PATTERNS	[ftp://]geoff.biop.ox.ac.uk/
PROPAT	[ftp://]ftp.mdc-berlin.de/
SOM	[ftp://]ftp.mdc-berlin.de/pub/neural
SEARCHWISE	[ftp://]sable.ox.ac.uk/pub/users
PROFILE	[ftp://]ftp.ebi.ac.uk/pub/software/unix/
TPROFILESEARCH	[ftp://]ftp.ebi.ac.uk/pub/softare/vax/egcg
CAP	[ftp://]ncbi.nlm.nih.gov/pub/koonin/cap

Please amend the claims as follows:

9. (Amended) A method for identifying a population of bi-ligands to receptors in a receptor family, comprising

[(a) determining a common ligand to a conserved site in the receptor family;]

[(b)] **(a)** attaching an expansion linker to **[said]** **a** common ligand, **wherein said common ligand binds to a cofactor binding site and** wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity

site of a receptor in said receptor family, to form a module, **wherein said receptor is an enzyme**; **[and]**

[(c)] **(b)** generating a population of bi-ligands, wherein said bi-ligand comprises said module and a second ligand linked by said expansion linker**[.]** ;

(c) screening said population of bi-ligands for binding to a receptor in said receptor family;

(d) identifying a bi-ligand that binds to and has specificity for said receptor; and

(e) repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second receptor in said receptor family.

11. (Amended) The method of claim 9, wherein said receptor **in said receptor family** is an enzyme selected from the group consisting of **a** kinase**[s]**, dehydrogenase**[s]**, oxidoreductase**[s]**, GTPase**[s]**, carboxyl transferase**[s]**, acyl transferase**[s]**, decarboxylase**[s]**, transaminase**[s]**, racemase**[s]**, methyl transferase**[s]**, formyl transferase**[s]**, and α-ketodecarboxylase**[s]**.

12. (Amended) The method of claim 9, wherein said receptor family binds a cofactor selected from the group

consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate, adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.